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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/487,558	01/19/2000	Robert Busby	109272.130	3300
26161	7590	04/07/2004	EXAMINER	
FISH & RICHARDSON PC 225 FRANKLIN ST BOSTON, MA 02110			LAMBERTSON, DAVID A	
			ART UNIT	PAPER NUMBER
			1636	

DATE MAILED: 04/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

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Office Action Summary

Application No.

09/487,558

Applicant(s)

BUSBY ET AL

Examiner

David A. Lambertson

Art Unit

1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 January 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 104-108, 113, 119-125, 131-137, 144-148 and 225-238 is/are pending in the application.
- 4a) Of the above claim(s) 120-125 and 131-137 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 104-108, 113, 119, 144-148 and 225-238 is/are rejected.
- 7) ☒ Claim(s) 113 and 230 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

Art Unit: 1636

DETAILED ACTION

Receipt is acknowledged of a reply to the previous Office Action, filed January 20, 2004. Amendments were made to the claims. Specifically, claims 1-103, 109-112, 114-118, 126-130, 138-143 and 149-224 are cancelled and new claims 237 and 238 are added.

Claims 104-108, 113, 119-125, 131-137, 144-148 and 225-238 are pending in the instant application. Claims 121-125 and 131-137 are withdrawn from consideration. Claims 104-108, 113, 119, 144-148 and 225-238 are under examination in the instant application. Any rejection of record in the previous Office Action, mailed July 15, 2003, that is not addressed in this action has been withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 144-148 and 232-236 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. **This rejection is maintained for the reasons set forth in the previous Office Action.**

It is noted that the entirety of the rejection as provided in the previous Office Action is not maintained. However, with regard to the instant claims, the rejection is

Art Unit: 1636

maintained because the claims require that a polyketides be “produced” rather than simply modulated. Thus one of skill in the art would need to be able to “produce” any endogenous polyketide simply by overexpressing or conditionally expressing CreA in a fungal cell. In order to do this, one of skill in the art would need to know if the production of any particular polyketide (chosen from a vast number of polyketides that are endogenous to the cell) was increased versus decreased. In the instant case, it is clear that the production of all given endogenous polyketides is not necessarily increased. For instance, one of skill in the art would not use the method to produce the polyketides Erdin because, as set forth in the declaration by E. Diggers, Ph.D., the production of Erdin is decreased upon the overexpression of CreA. Thus, when confronted with the instant method, the skilled artisan would be left to guess which polyketides could be produced using the claimed method, and which could not be produced. This represents a great deal of unpredictability, which was established in the previous Office Action, and will be reiterated below in response to the relevant arguments made by Applicant.

Response to Arguments Concerning Claim Rejections - 35 USC § 112

Applicant's arguments filed January 20, 2004 have been fully considered but they are not persuasive. Applicant provides the following remarks in traversal of the previous Office Action; it is noted that only those arguments that pertain to the portion of the rejection that is maintained are addressed below, as all of the other arguments are rendered moot by the dropping of that aspect of the rejection:

1. Applicant argues that the Declaration provided by Dr. Edward Diggers provides sufficient detail to show altered polyketide production. Importantly, Applicant asserts

Art Unit: 1636

that the declaration demonstrates that the overexpression of CreA in *P. citrinum* results in increased production of compactin, and that geodin and lovastatin production were increased in an *A. terreus* strain overexpressing CreA.

2. Applicant further asserts that, although two of the eight polyketides specifically listed in the results shown in the declaration by Dr. E. Diggers were decreased in production, the skilled artisan would recognize that it would be useful to decrease the production of a given polyketides in order to conserve resources for the production of a different polyketides.

Applicant's arguments have been considered, but are not found to be persuasive for the following reasons.

1. The previous Office Action cited Parekh, which made several relevant points on the matter of metabolic engineering (see page 5 of the previous Office Action). First, Parekh indicated that metabolic engineering requires a great deal of precision because unknown mechanisms of feedback inhibition can have adverse effects on the metabolic engineering process. Parekh then goes on to summarize that, with limited knowledge of the effects associated with the production of a particular molecule of interest, one is often left with an undue and unpredictable empirical experimentation process. This is clearly the case as it regards the overexpression of CreA, as it results in the increased production of some polyketides, but the reduced production of others. Given the teachings in the instant specification (and the broad scope of the claims), one would be led to believe that any endogenous polyketide could have its production increased simply by overexpressing CreA in a fungal host cell. However, this is clearly not the case, as evidenced by the declaration of Dr. E. Diggers, which indicates that CreA overexpression has adverse

Art Unit: 1636

effects on the production of some polyketides, such as Erdin and Osoic. Thus, one of skill in the art would be left to empirically determine which polyketides could be produced by the claimed method, and which could not be produced. As such, the claimed method cannot be considered enabled for the production of just any polyketide.

2. While it may be useful to decrease the production of a particular polyketide in order to enhance the production of another, this reads on the *modulation* of that polyketide and not its *production*. The purpose of the rejected claims however, is to produce a given polyketide. As discussed above, however, the overexpression of CreA does not result in the production of just any polyketide, as at least Erdin and Osoic are decreased in abundance following overexpression of CreA. This would lead one of skill in the art to question which polyketides can be produced by the method. However, neither the specification nor the prior art clearly delineates which polyketides are subject to up-regulation by CreA or its downstream targets, thus the skilled artisan would be required to practice undue and unpredictable empirical experimentation in order to determine which polyketides can be produced using the claimed method.

In the instant case, the broad scope of polyketides that is claimed as capable of being made is not enabled, evidenced by the Declaration of Dr. E. Diggers. The skilled artisan is given no guidance in the specification with regard to which polyketides experience an increase versus a reduction in production upon the overexpression of CreA. The prior art establishes that metabolic engineering is unpredictable because one cannot be sure of what endogenous feedback inhibition mechanisms will be triggered, thereby abrogating the production of the given polyketide. Given these teachings, the skilled artisan would not be capable of predicting which polyketides could be produced using the

Art Unit: 1636

claimed method. As a result, the method is not enabled for the production of just any polyketide in a fungal cell, and the rejection is maintained in this aspect.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 104-108, 119, 144-147, 225-229, 231-235, 237 and 238 are rejected under 35 U.S.C. 102(b) as being anticipated by Fillinger *et al.* (*FEBS Letters* **368**: 547-550, 1995; see entire document; henceforth Fillinger). **This is new rejection as necessitated by amendment.**

This rejection is predicated on the fact that the only step necessary in the method for the modulation or production of a polyketide is the overexpression of CreA in a fungal cell. Since the polyketides that are produced must be endogenous to the cell, any cell that overexpresses CreA will necessarily produce and modulate such polyketides. In the instant case, one such endogenous polyketide would be the statin, lovastatin.

Fillinger teaches the overexpression of CreA in the Ascomycetes, *A. nidulans*. Specifically, Fillinger describes a genetically modified *A. nidulans* strain that contains multiple copies of the CreA gene under the control of a regulatable promoter (see for example page 548, section 3.2). The expression of the gene is carried out under non-induced as well as induced conditions, meaning that the expression of the CreA gene is conditionally overexpressed/repressed (see for example page 548, section 3.2).

Art Unit: 1636

Therefore, when the host cell described by Fillinger is grown under inducing conditions, the claimed method is inherently being practiced because the only method step set forth in the claims is being performed. As a result, and absent any evidence to the contrary, the host cell must necessarily produce/modulate the production of lovastatin, as well as a number of other polyketides such as mevinolin and monacolin, thereby anticipating the claimed methods.

Allowable Subject Matter

Claims 113 and 230 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Lambertson whose telephone number is (571) 272-0771. The examiner can normally be reached on 6:30am to 4pm, Mon.-Fri., first Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Art Unit: 1636

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David A. Lambertson, Ph.D.
AU 1636



JAMES KETTER
PRIMARY EXAMINER